# PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY



To:

see form PCT/ISA/220

## WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
*(day/month/year)* see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

**FOR FURTHER ACTION**
See paragraph 2 below

| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
|---|---|---|
| PCT/IB2005/001140 | 25.04.2005 | 06.05.2004 |

International Patent Classification (IPC) or both national classification and IPC
C07D207/16, C07D211/26, C07D211/60, C07D211/96, C07D265/30, A61K31/401, A61K31/445, A61K31/5375

Applicant
PFIZER INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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**Box No. I Basis of the opinion**

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 14,15 with respect to industrial applicability

because:

☒ the said international application, or the said claims Nos. 14, 15 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination *(specify)*:

**see separate sheet**

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

| | | |
|---|---|---|
| the written form | ☐ | has not been furnished |
| | ☐ | does not comply with the standard |
| the computer readable form | ☐ | has not been furnished |
| | ☐ | does not comply with the standard |

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

**Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Yes: | Claims | 11,12 |
| | No: | Claims | 1-10,13-15 |
| Inventive step (IS) | Yes: | Claims | 11,12 |
| | No: | Claims | 1-10, 13-15 |
| Industrial applicability (IA) | Yes: | Claims | 1-13 |
| | No: | Claims | |

2. Citations and explanations

**see separate sheet**

**Box No. VI Certain documents cited**

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

**see form 210**

**Re Item III.**

Claims 14-15 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

**Re Item V.**

1. Reference is made to the following documents:

D1 : WO 00/33788 A (AMERICAN BIOGENETIC SCIENCES INC; UNIVERSITY COLLEGE DUBLIN; SZMUSZKOV) 15 June 2000 (2000-06-15)

D2 : BIN HO, PRABHA M. VENKATARANGAN, SHARON F. CRUSE ET AL.: "Synthesis of 2-piperidinecarboxylic acid derivatives as potential anticonvulsants" EUR. J. MED. CHEM., vol. 33, 1998, pages 23-31, XP002348704

D3 : MIN SHEN, ARNAUD LETIRAN, YUNDE XIAO, ALEXANDER GOLBRAIKH, HAROLD KOHN, ALEXANDER TROPSHA: "Quantitative Structure-Activity Relationship Analysis of Functionalized Amino Acid Anticonvulsant Agents Using k Nearest Neighbor and Simulated Annealing PLS Methods" J. MED. CHEM., vol. 45, 2002, pages 2811-2823, XP002348705

D4 : US 3 931 139 A (WISSMANN ET AL) 6 January 1976 (1976-01-06)

D5 : BOULOS ZACHARIE, NANCIE MOREAU, CHRISTOPHER DOCKENDORFF: "A Mild procedure for the Reduction of Pyridine N-Oxides to Piperidines Using Ammonium Formate" J. ORG. CHEM., vol. 66, 2001, pages 5264-5265, XP002348706

D6 : WO 02/18335 A (YAMANOUCHI PHARMACEUTICAL CO., LTD; TORAY INDUSTRIES, INC; MORIHIRA, K) 7 March 2002 (2002-03-07)

D7 : VIDYADHAR S. RANADE, ROEL PRINS: "Diastereoselective Hydrogenation of (S)-Proline-2-methylanilide" JOURNAL OF CATALYSIS, vol. 185, 1999, pages 479-486, XP002348707

D8 : TSUTOMU MIMOTO, RYOHEI KATO, HARUO TAKAKU, SATOSHI NOJIMA,

KEISUKE TERASHIMA ET AL.: "Structure-Activity Relationship of Small-Sized HIV Protease Inhibitors Containing Allophenylnorstatine" J.MED. CHEM., vol. 42, 1999, pages 1789-1802, XP002348708

D9 : STEVEN K. DAVIDSEN, PAUL D. MAY, JAMES B. SUMMERS: "Di-tert-butyl N-Acylimidodicarbonates as Isolable Acylating Agents: Mild Conversion of Primary Carboxamides to Substituted Amides" J. ORG. CHEM., vol. 56, 1991, pages 5482-5485, XP002348709

D10 : JOSEPH L. DUFFY, NANCY J. KEVIN, BRIAN A. KIRK, KEVIN T. CHAPMAN, WILLIAM A. SCHLEIF ET AL.: "Synthesis and Activity of Novel HIV Protease Inhibitors with Improved Potency Against Multiple PI-Resistant Viral Strains" BIOORGANIC &; MEDICINAL CHEMISTRY LETTERS, vol. 12, 2002, pages 2423-2426, XP002348710

D11 : JU YOUNG LEE, YONG JUN CHUNG, YOE-SIK BAE, SUNG HO RYU, BYEANG HYEAN KIM: "Synthesis of hexapeptide and tetrapeptide analogues of the immunomodulating peptides" J. CHEM. SOC. PERKIN TRANS. 1, 1998, pages 359-365, XP002348711

D12 : KOICHI KAWASAKI, KATSUHIKO HIRASE, MASANORI MIYANO, TOSHIKI TSUJI, MASANORI IWAMOTO: "Amino Acids and Peptides XVI. Synthesis of N-Terminal Tetrapeptide Analogs of Fibrin a-Chain and Their Inhibitory Effects on Fibrinogen/Thrombin Clotting" CHEM. PHARM. BULL., vol. 40, no. 12, 1992, pages 3253-3260, XP001207622

D13 : HAE YOON RHYOO, YOUNG-AE YOON, HEE-JUNG PARK, YOUNG KEUN CHUNG: "Use of amino amides derived from proline as chiral ligands in the ruthenium(II)-catalyzed transfer hydrogenation reaction of ketones" TETRAHEDRON LETTERS, vol. 42, 2001, pages 5045-5048, XP002348712

D14 : SHU KOBAYASHI, HIROMI UCHIRO, YUKO FUJISHITA, ISAMU SHIINA, TERUAKI MUKAIYAMA: "Asymmetric Aldol Reaction between Achiral Silyl Enol Ethers and Achiral Aldehydes by Use of a Chiral Promoter System" J. AM. CHEM. SOC., vol. 113, 1991, pages 4247-4252, XP002348776

D15 : MAKOTO NAKAJIMA, IRIE MIYOSHI, KUMIKO KANAYAMA, SHUN-ICHI HASHIMOTO: "Enantioselective Synthesis of Binaphthol Derivatives by Oxidative Coupling of Naphthol Derivatives Catalyzed by Chiral Diamine-

Copper Complexes" J. ORG. CHEM., vol. 64, 1999, pages 2264-2271, XP002348777

D16 : DATABASE CROSSFIRE BEILSTEIN Beilstein Institut zur Förderung der Wissenschafter, Frankfurt am Main, DE; 1995, XP002348720 Database accession no. 7305927 (BRN)

D17 : DATABASE CROSSFIRE BEILSTEIN Beilstein Institut zur Förderung der Wissenschafter, Frankfurt am Main, DE; 1988, XP002348721 Database accession no. 179894 (BRN)

D18 : DATABASE CROSSFIRE BEILSTEIN Beilstein Institut zur Förderung der Wissenschafter, Frankfurt am Main, DE; 1994, XP002348722 Database accession no. 6399577 (BRN)

D19 : DATABASE CROSSFIRE BEILSTEIN Beilstein Institut zur Förderung der Wissenschafter, Frankfurt am Main, DE; 2000, XP002348723 Database accession no. 8412429 (BRN)

D20 : DATABASE CROSSFIRE BEILSTEIN Beilstein Institut zur Förderung der Wissenschafter, Frankfurt am Main, DE; 1988, XP002348724 Database accession no. 17092 (BRN)

D21 : EP 0 564 924 A (MILES INC; BAYER CORPORATION) 13 October 1993 (1993-10-13)

Present claims 1 and 6 relate to an extremely large number of possible compounds, in particular in view of the broad definitions of the groups T and $R^1$. Support within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be reasonably supported and disclosed, namely those parts wherein both T and $R^1$ are reasonably defined, i.e. the compounds wherein T is defined as found in claim 7 and $R^1$ is defined as found in claim 9.

An attempt to search claims 1 and 6 in their full scope resulted in a very huge number

of results (many thousand relevant compounds) so that a meaningful search over the complete scope of claims 1 and 6 cannot reasonably be carried out. Thus the search report can only be considered complete for the compounds and use thereof wherein T and $R^1$ are defined as indicated above, and the compounds and methods cited against the novelty of claims 1-9 are exemplary only.

2. The subject matter defined in claims 1-10 is not novel (Art. 33(2) PCT). The prior art discloses numerous compounds which fall withun the scope of claims 1-10, cf. the relevant passages cited in the search report.

   D1 discloses compounds corresponding to claims 1-9 for the treatment of dementia. The subject matter of claims 13-15 lacks novelty in view of this disclosure. Documents D2 and D3 also disclose the therapeutic use of compounds corresponding to claims 1-9 and thus are novelty destroying for the subject matter of claim 13.

   D21 discloses, in general form, compounds corresponding to claims 1-9 and the use thereof for the treatmet of diabetes and inflammatory diseases. The subject matter of claims 1-9 and 12-15 therefore is obvious in view of this disclosure (Art. 33(3) PCT).

   The use of compounds as defined in claim 10 as medicaments is not derivable from the cited prior art and may be considered inventive.

3. For the assessment of the present claims 14 and 15 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.